ABSTRACT OF THE DISCLOSURE

The present invention provides a genetic method for tethering polypeptides to the yeast cell wall in a form accessible for binding to macromolecules. Combining this method with fluorescence-activated cell sorting provides a means of selecting proteins with increased or decreased affinity for another molecule, altered specificity, or conditional binding. Also provided is a method for genetic fusion of the N terminus of a polypeptide of interest to the C-terminus of the yeast Aga2p cell wall protein. The outer wall of each yeast cell can display approximately 10^4 protein agglutinins. The native agglutinins serve as specific adhesion contacts to fuse yeast cells of opposite mating type during mating. In effect, yeast has evolved a platform for protein-protein binding without steric hindrance from cell wall components. As one embodiment, attaching an scFv antibody fragment to the Aga2p agglutinin effectively mimics the cell surface display of antibodies by B cells in the immune system for affinity maturation in vivo. As another embodiment, T cell receptor mutants can be isolated by this method that are efficiently displayed on the yeast cell surface, providing a means of altering T cell receptor binding affinity and specificity by library screening.